

MALARIA

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Infectious Diseases

Objectives

- Importance of malaria to the military
- Pathophysiology, host parasite relationships and life cycle of *Plasmodium* species
- Clinical manifestations of malaria
- Laboratory and diagnostic tests
- Treatment and prevention

Malaria

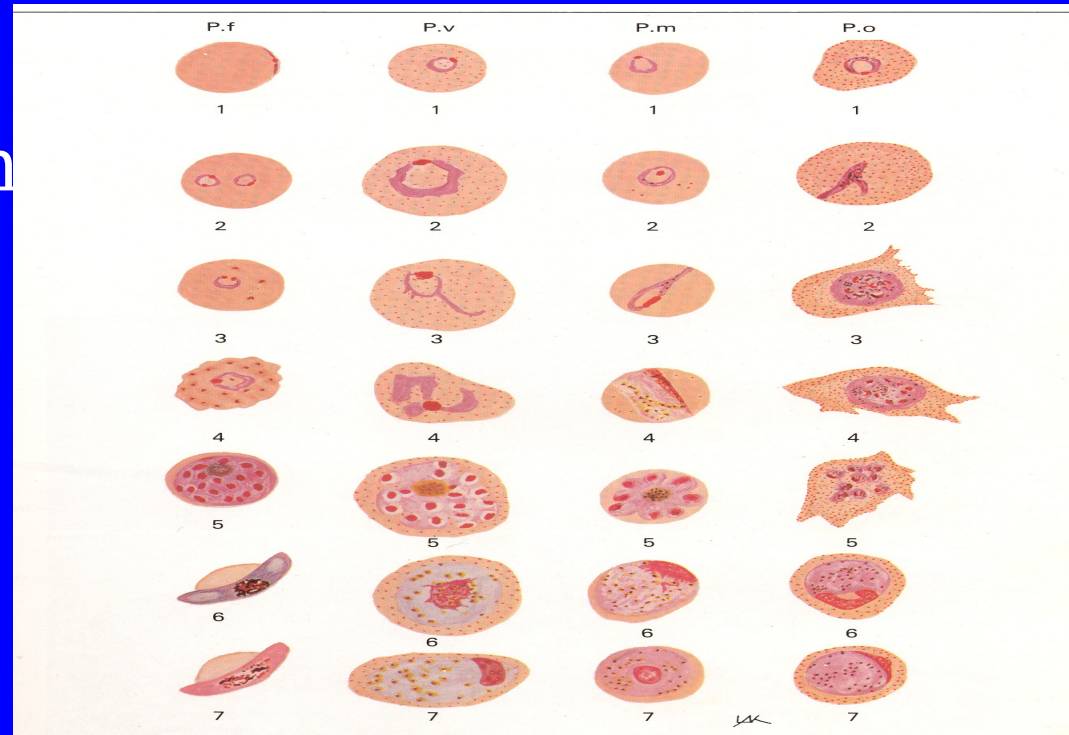
- Malaria – “bad air” from the marshes
- Splenomegaly with fever
 - Nei Ching Canon of Medicine (China 1700 BC)
 - Ebers Papyrus (Egypt 1570 BC)
- Endemic in US during 18th & 19th centuries
- 200 – 300 million cases worldwide per year
- 1 – 2 million deaths worldwide per year

MALARIA

- Genus: Plasmodium

- Species:

- falciparum
- vivax
- ovale
- malariae



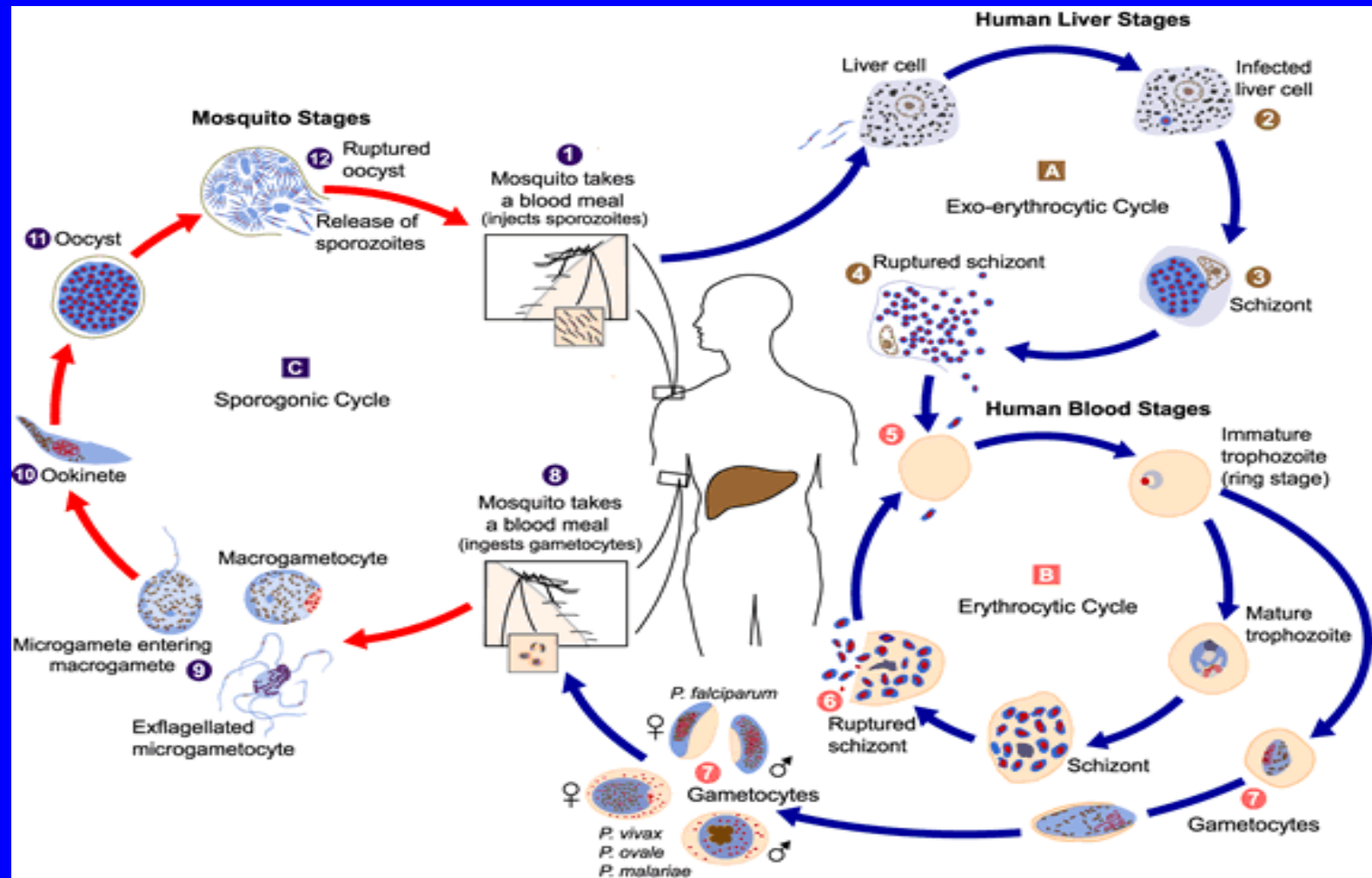
LIFE CYCLE

- Vector Phase: Anopheles mosquito



- Host Phase: Human and Simian
 - Exoerythrocytic (liver)
 - Erythrocytic (RBC)

Life Cycle



INCUBATION

- *P. falciparum*: 10 days - 3 months
- *P. vivax*: 2 weeks - 12 months
- *P. ovale*: 2 weeks - 12 months
- *P. malariae*: 5 weeks - 3 years
- Seasonal variability with temperate climates

CLINICAL ASPECTS

- Release of merozoites from red cell lysis
- Malarial cycle:
 - cold or chilling stage
 - hot stage
 - sweating stage
 - resting stage



Fever Periodicity

- Synchronized release of merozoites
- *P. vivax* - tertian
- *P. malariae* - quartan
- *P. falciparum* - tertian
- Takes 1-2 weeks for non-immune patients
- Rare non-endemic areas

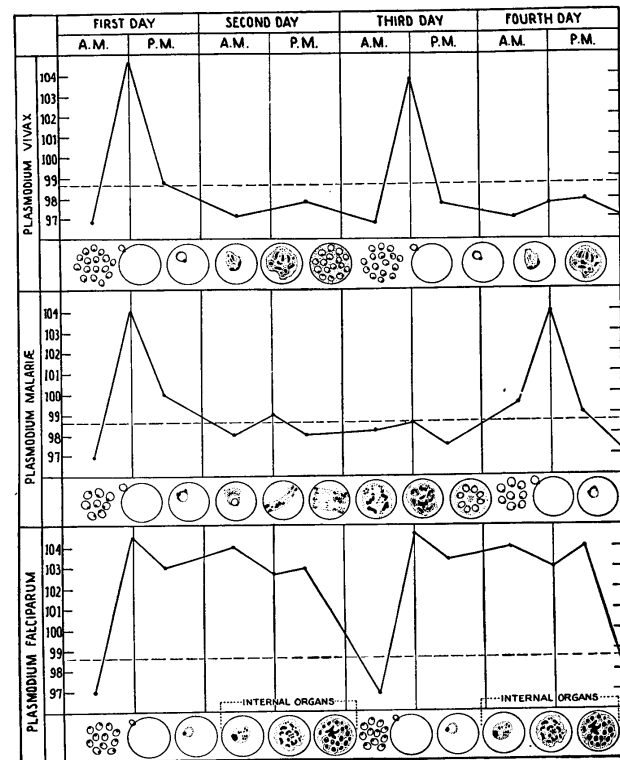


FIG. 31. Temperature curves in malaria showing relation to growth and schizogony of malarial parasites.

Recurrent and Persistent Infections

- Relapse
 - Dormant (hypnozoite) stages in liver
 - Only *P. vivax* and *P. ovale*
- Recrudescence
 - Incomplete treatment or partially effective host immune responses
 - Occurs with any of the four species, but most frequently with *P. falciparum*

Recurrent and Persistent Infections

- Reinfection
 - Areas of intense transmission
 - Most frequently with *P. falciparum*
- Multiple infections
 - Areas of intense transmission
 - Sub-Saharan Africa
- Persistent infection
 - *P. malariae*
 - Infection below detectable levels for 20 - 30 years

TARGETED RBCs

- Young RBCs - *P. vivax* and *P. ovale*
- Old RBCs - *P. malariae*
- Old and young - *P. falciparum*

LABORATORY FINDINGS

- Positive thick and thin smear
- Reflection of degree of hemolysis
 - ↓ Hemoglobin, hematocrit, haptoglobin
 - ↑ lactic dehydrogenase, reticulocytes
 - Thrombocytopenia
 - *P. falciparum*:
 - proteinuria, hemoglobinuria, ↑ serum creatinine, hypoglycemia

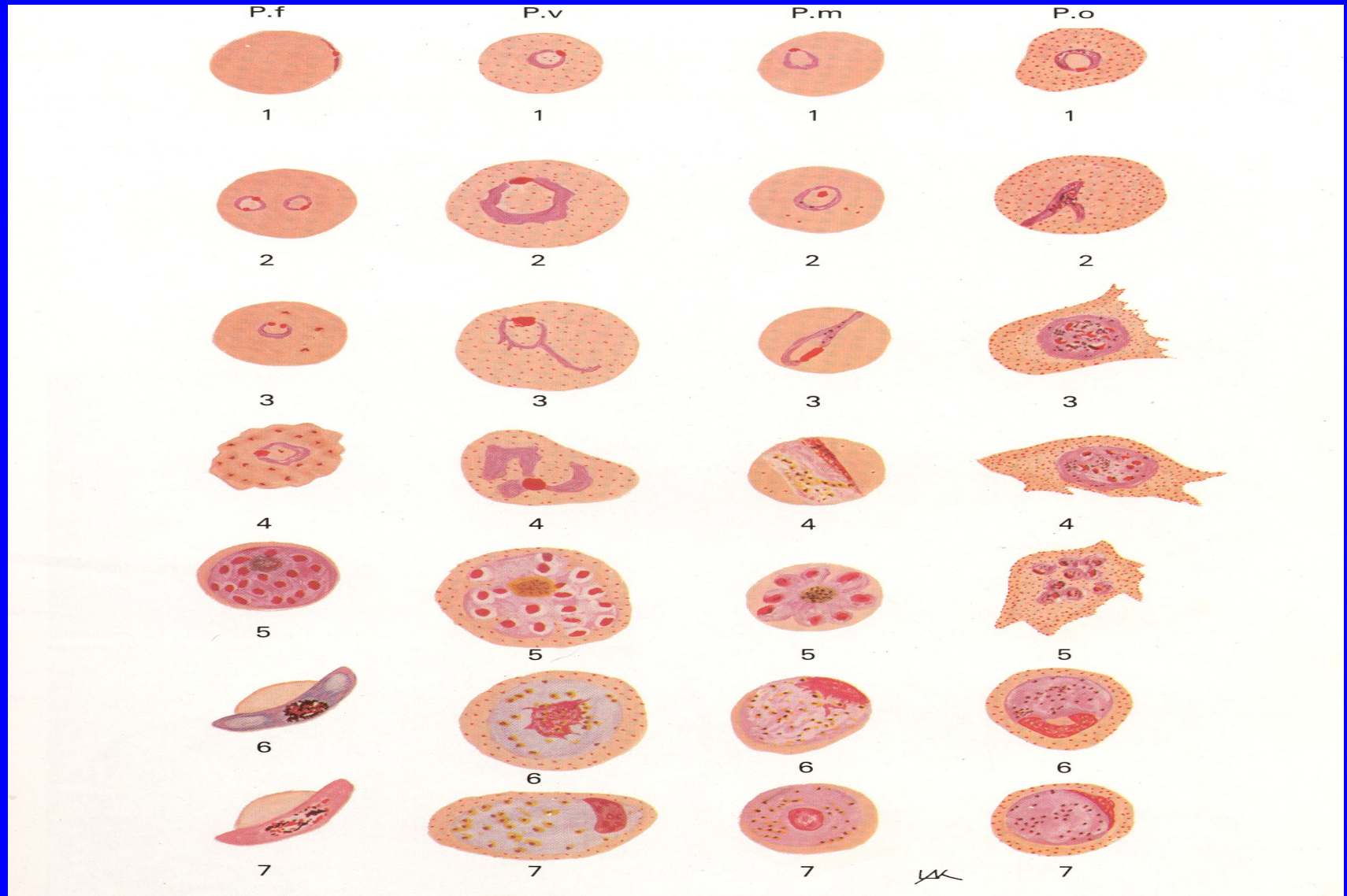
DIAGNOSIS

- Thick and thin smears - Gold Standard
 - Most reliable and least expensive (\$0.02)
- Quantitative Buffy Coat (\$0.83)
- Acridine orange stain (\$0.06)
- Parasight®-F test - (\$2.25)
- Serology
 - Not for acute cases

BLOOD SMEARS

- Thick and thin smears
 - 98% sensitive
 - 100% specific
 - species specific
- QBC
 - 95% sensitive
 - 100% specific
 - more rapid, not species specific

Plasmodium Species



Differential Diagnosis – Peripheral Smear

	<i>P. falciparum</i>	<i>P. vivax</i> & <i>P. ovale</i>
Multiply-infected RBCs	Common	Rare
Mature parasites (trophozoites and schizonts)	Absent	Common
RBC enlargement	Absent	Common

Plasmodium vivax

- Predominant: Latin America,
Indian Sub-continent
- Common: South America, Oceania
Southeast Asia
- Rare: Africa (lack of Duffy Coat antigen)

RBC Enlargement

- Present in *P. vivax*
- Absent in *P. falciparum*
- Schufner's dots
- 24 merozoites per schizont

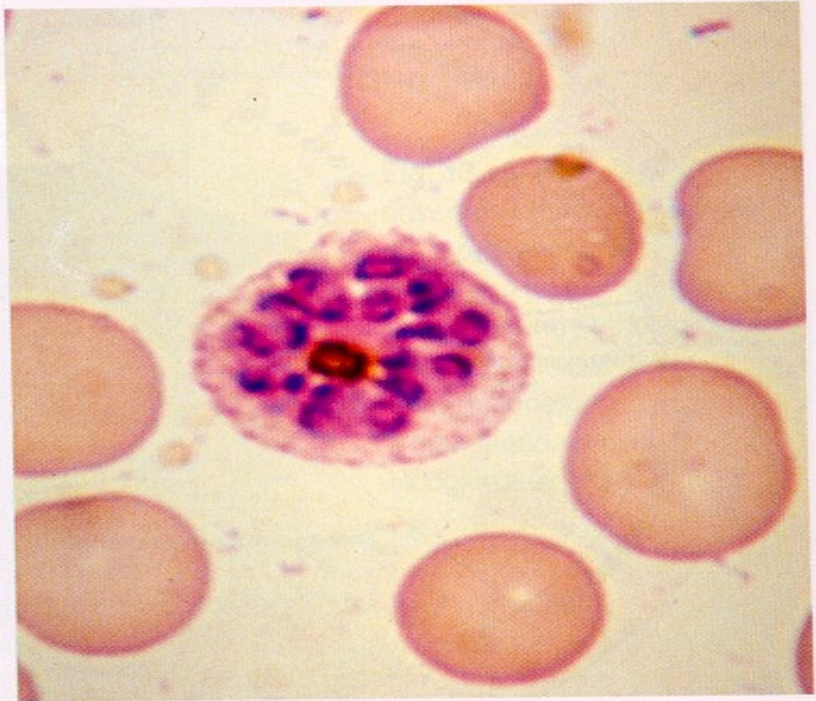
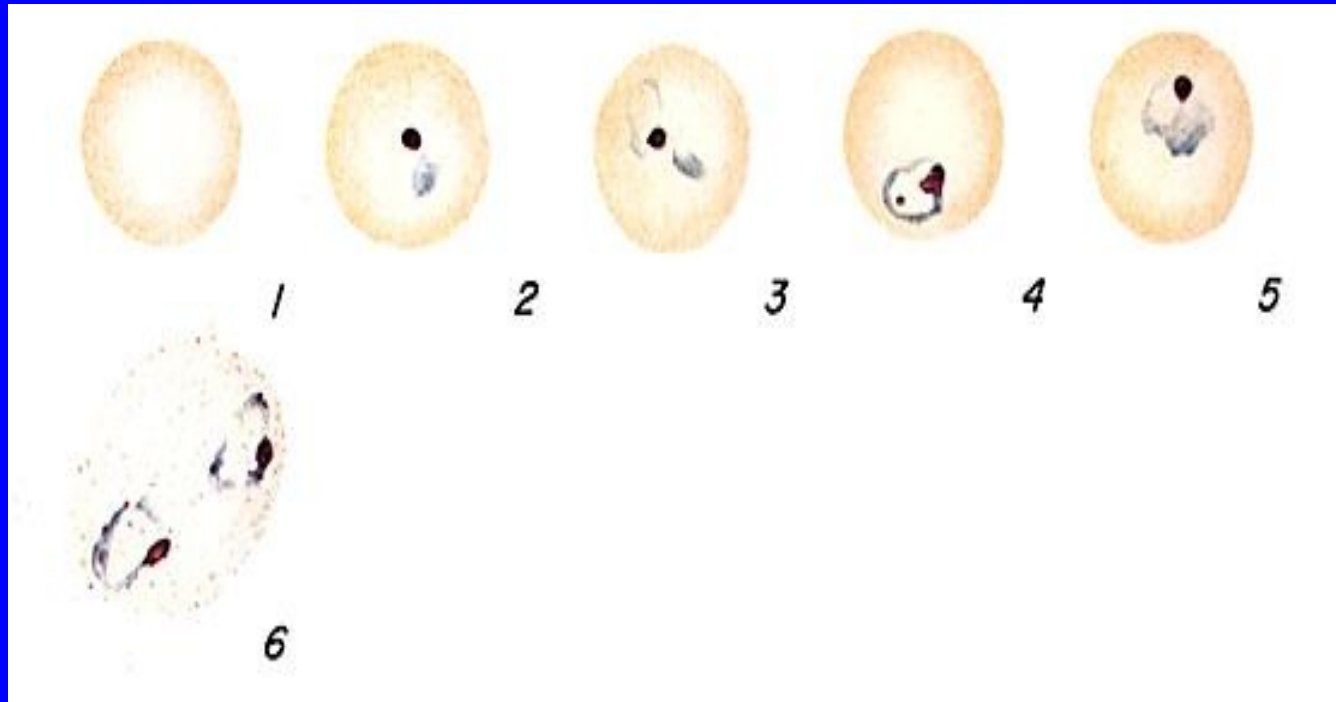
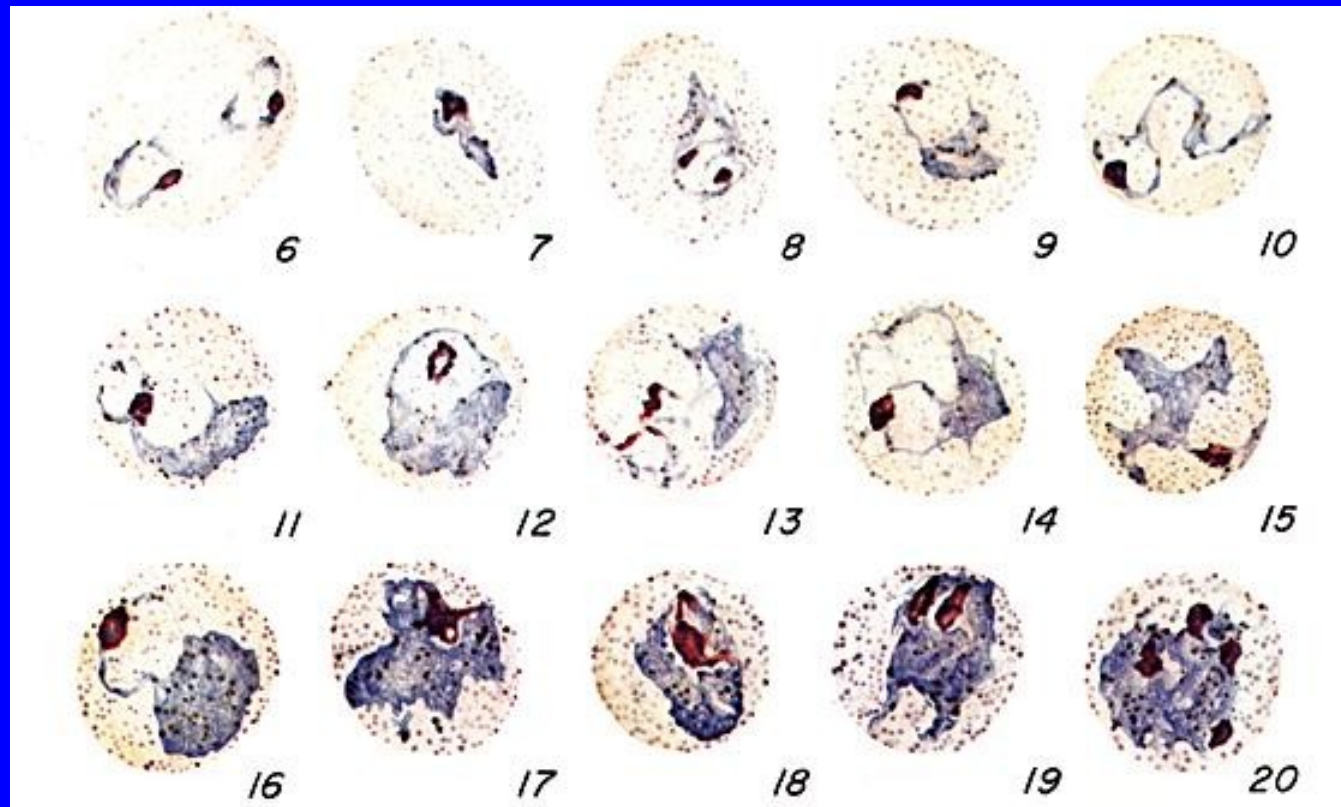


Fig. 13.26 Malaria. Thin blood film showing fully developed schizont of *P. vivax* with merozoites ready to burst out. Giemsa stain. See fig 13.21 for source.

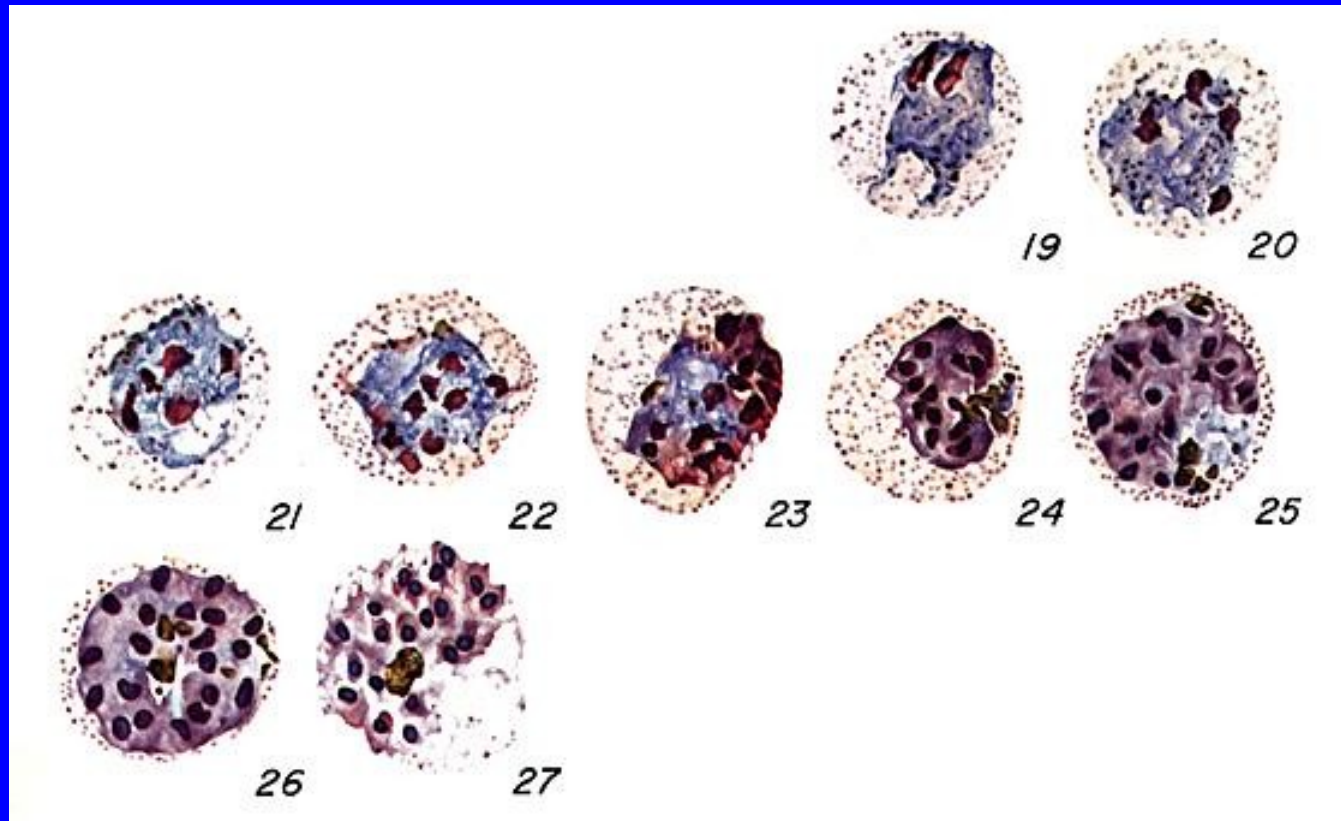
P. vivax ring



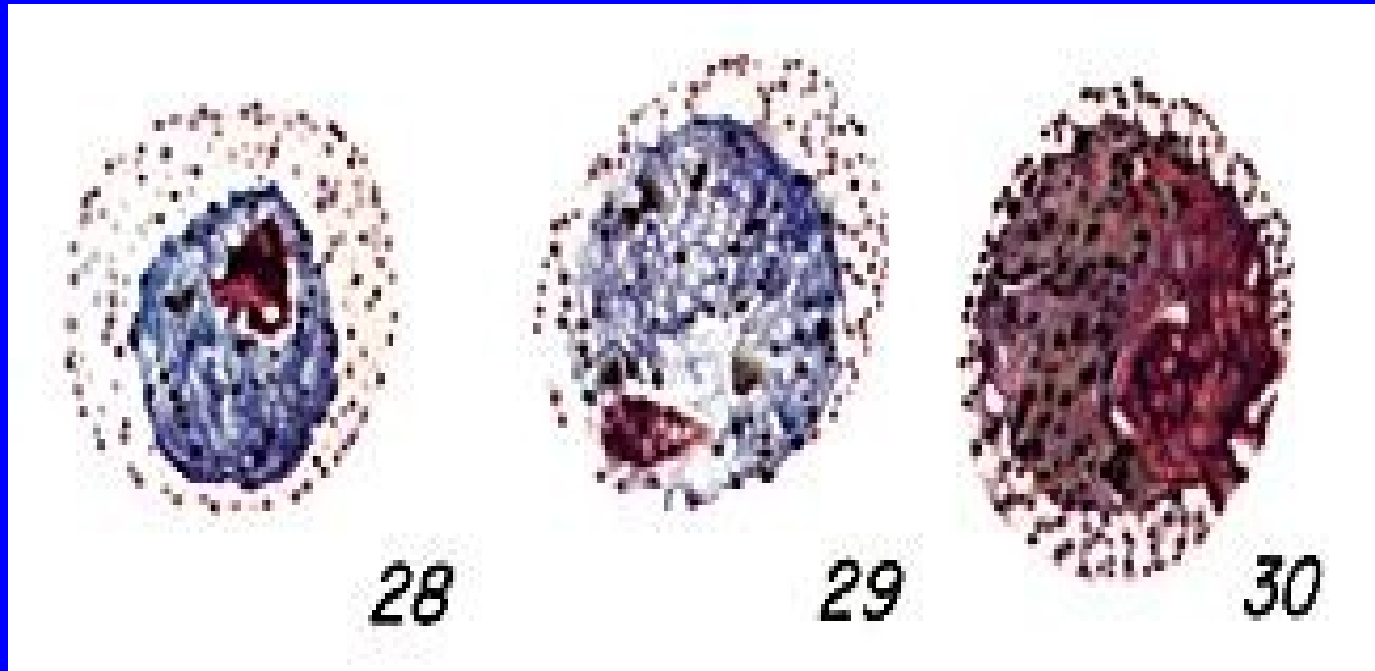
P. vivax trophozoites



P. vivax schizonts



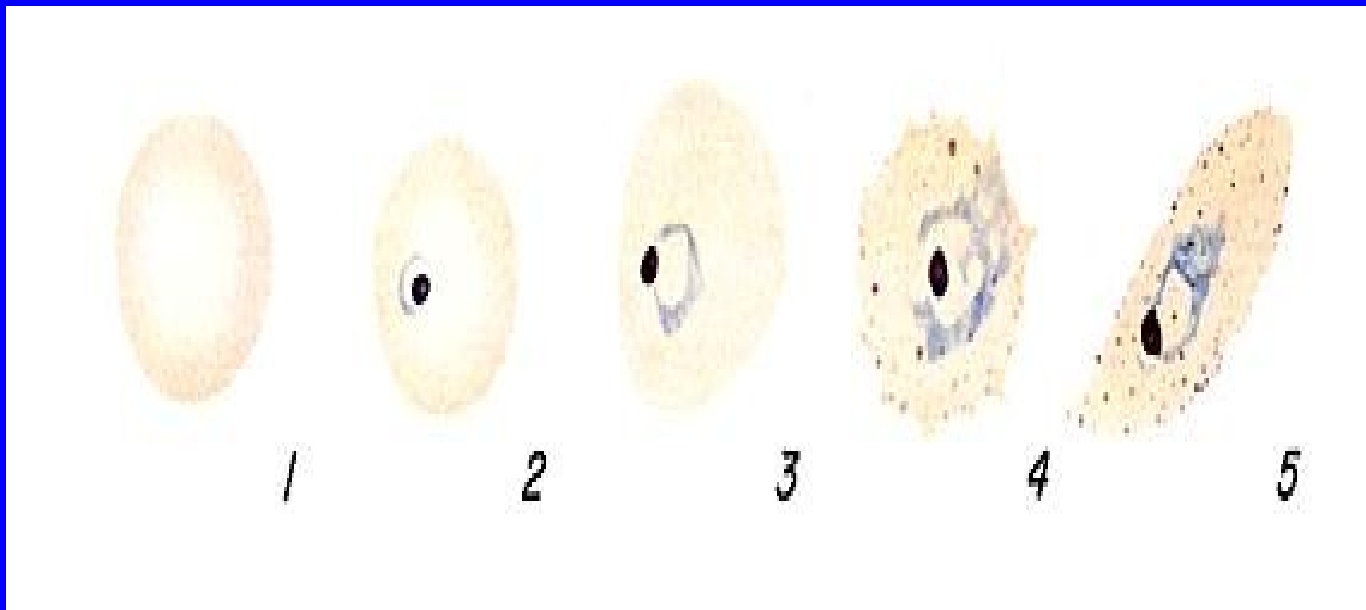
P. vivax gametocytes



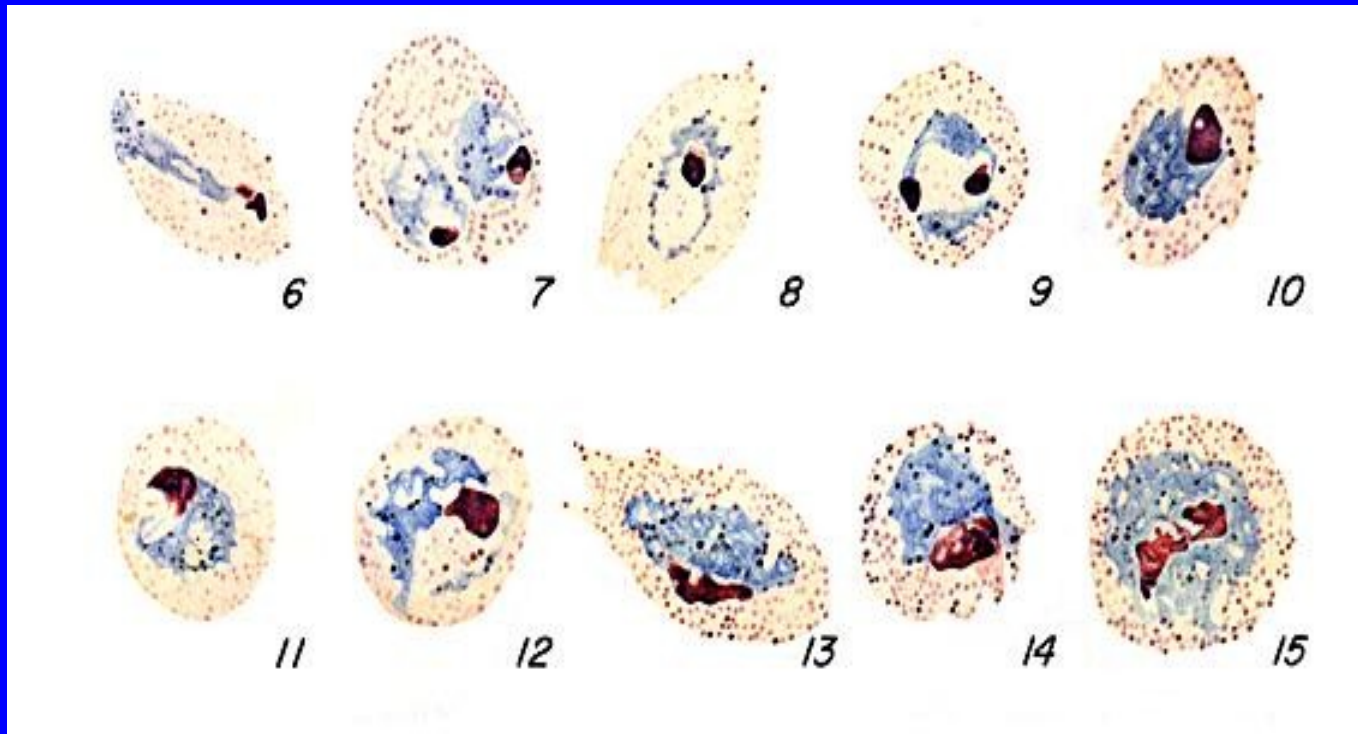
Plasmodium ovale

- Africa
- Early trophozoite – ring form
- Enlarged red blood cell and Schufner's dots
- Developing schizont with jagged edges: fimbriated
- Mature schizont with six merozoites

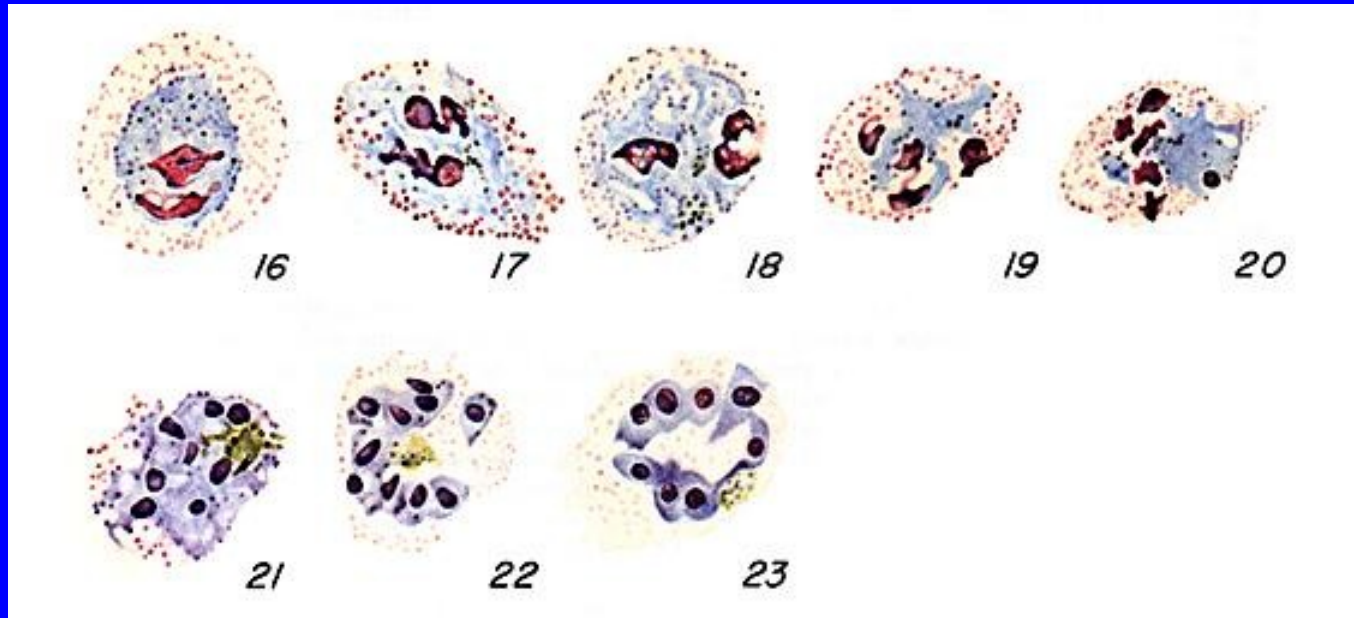
P. ovale ring



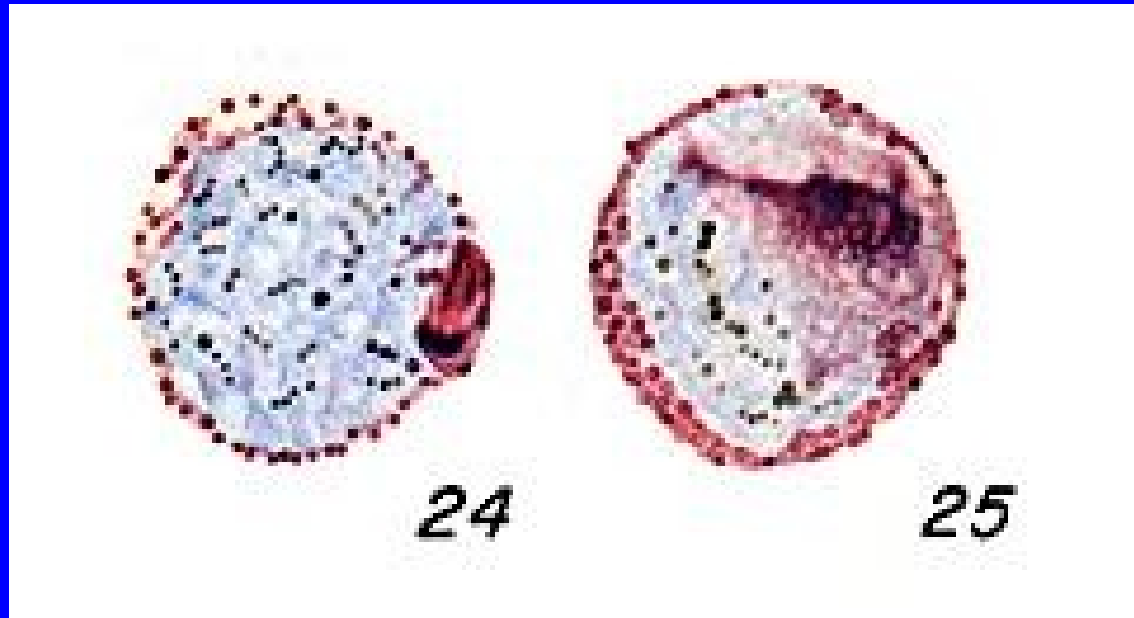
P. ovale trophozoite



P. ovale schizonts



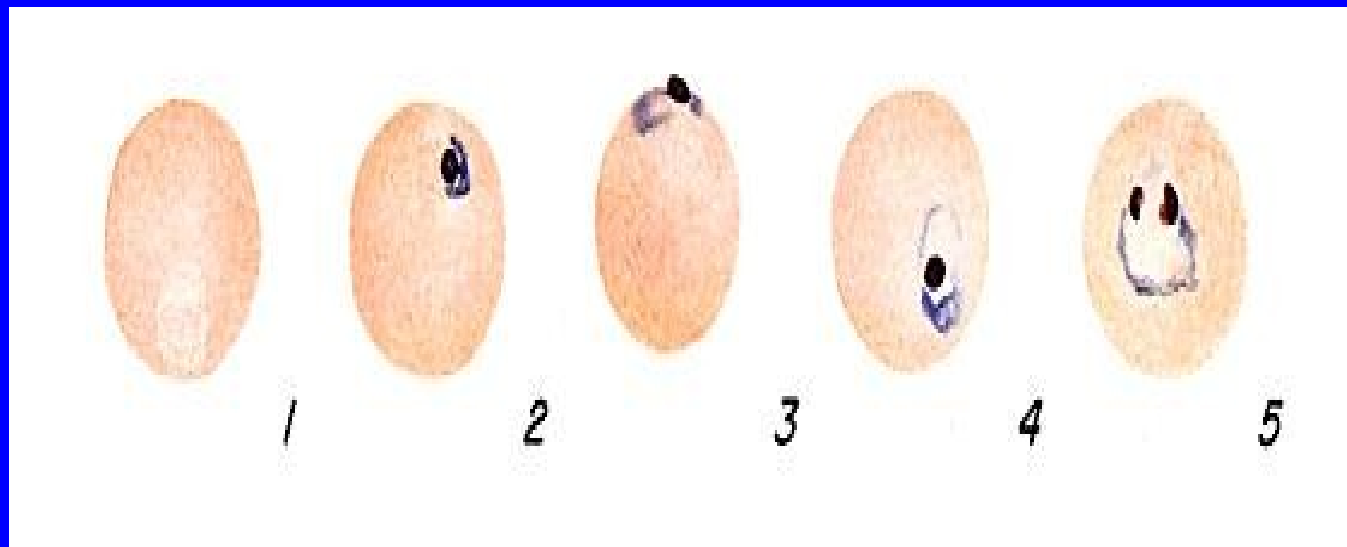
P. ovale gametocytes



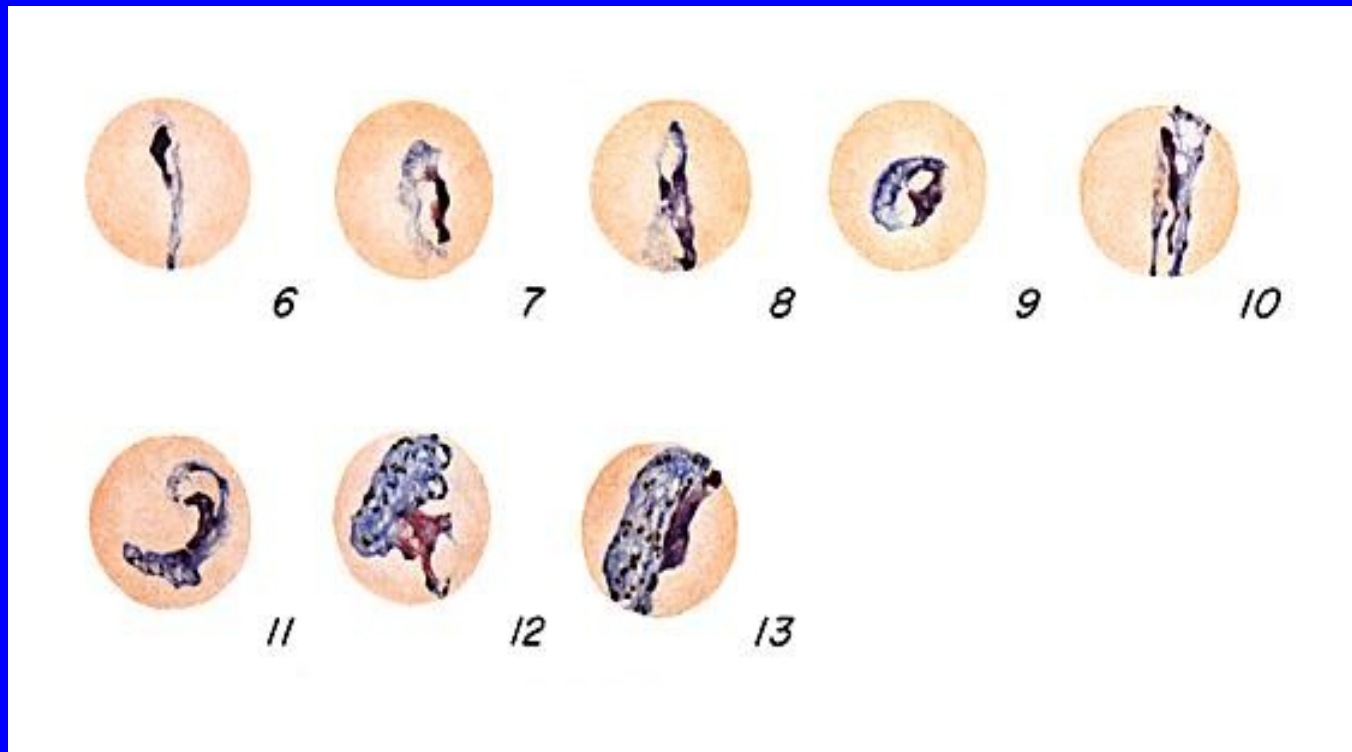
Plasmodium malariae

- Widespread
- Attacks older RBCs
- Late trophozoite with band form

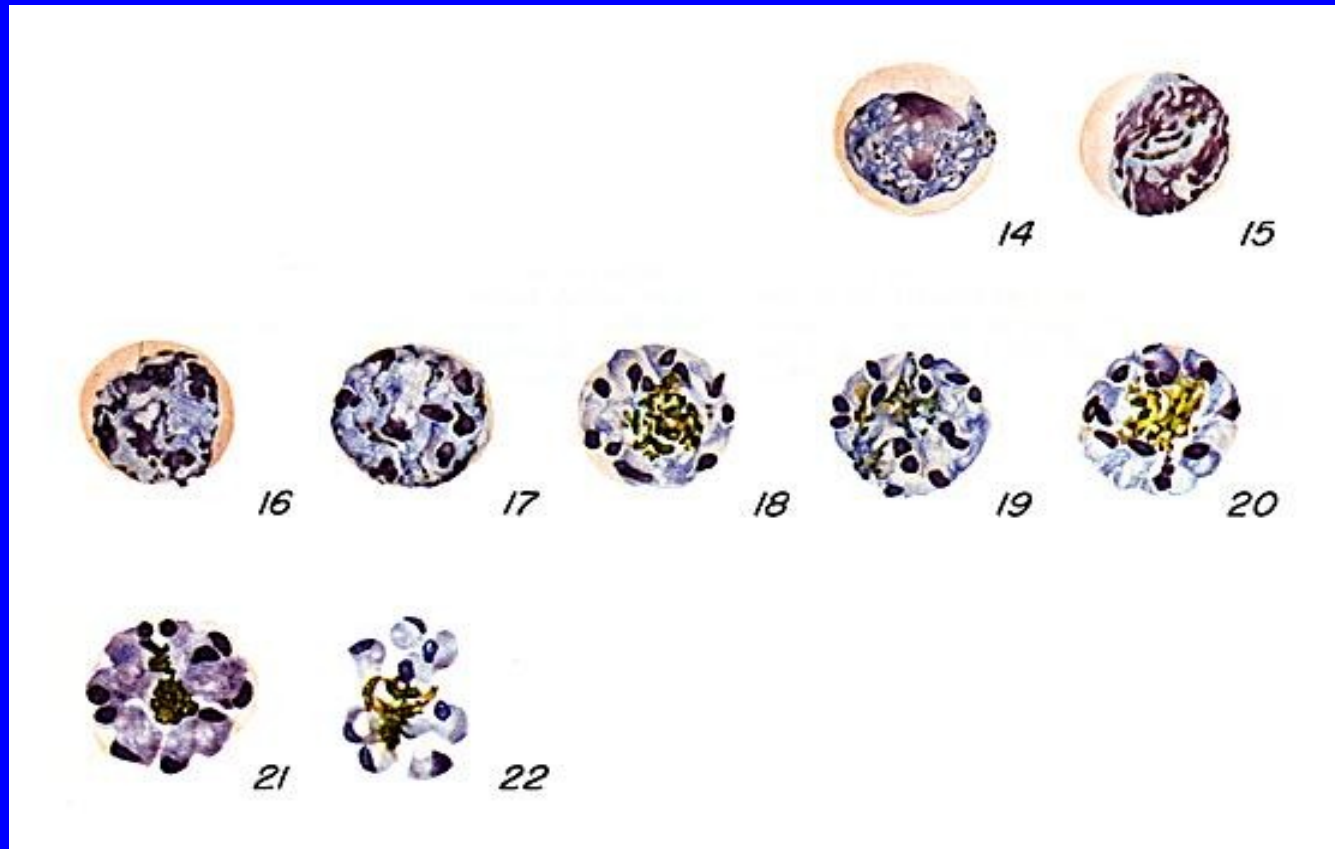
P. malariae ring stage



P. malariae trophozoite



P. malariae schizonts



P. malariae gametocytes



Plasmodium falciparum

- Predominant: Africa, Haiti
Papua New Guinea
- Common: South America, Oceania,
Southeast Asia

Mature Parasites in *P. falciparum*

- Present in heavy parasitemia
- Multiple ring forms in RBC
- Appliqué forms
- Delicate ring forms
- Banana-shaped gametocytes

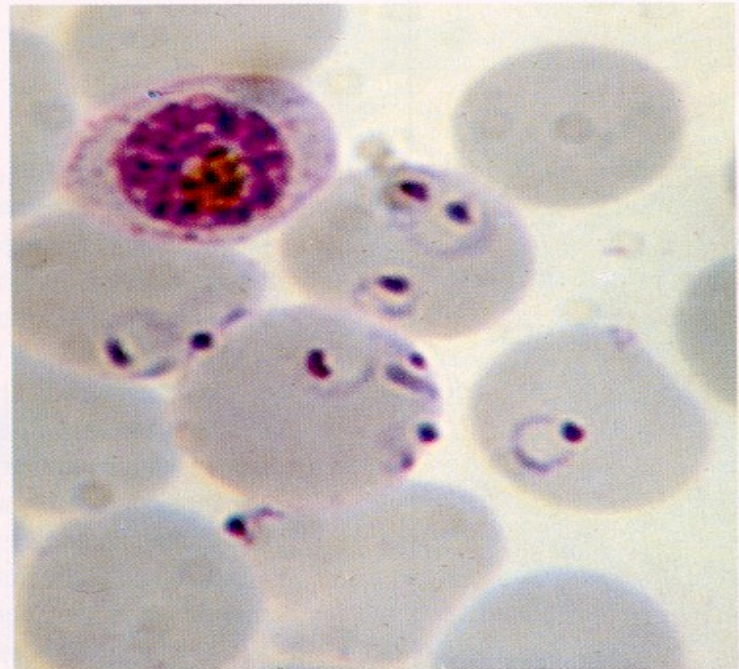


Fig. 13.25 Malaria. Thin blood film showing several ring forms and a schizont of *P. falciparum*. This is only seen in severe cases. Giemsa stain. See fig 13.21 for source.

RBC Enlargement

- Absent in *P. falciparum*
- Lack of schizonts
- Attacks RBCs of all ages
- Sequesters in the capillaries
- Brain & kidney damage

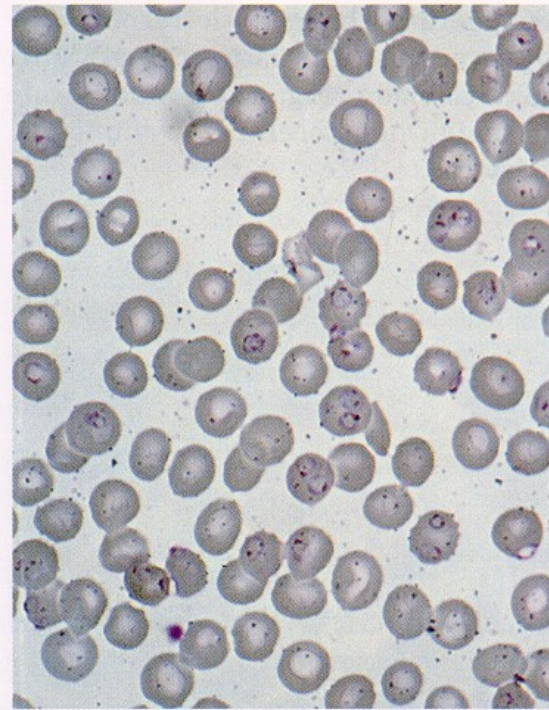
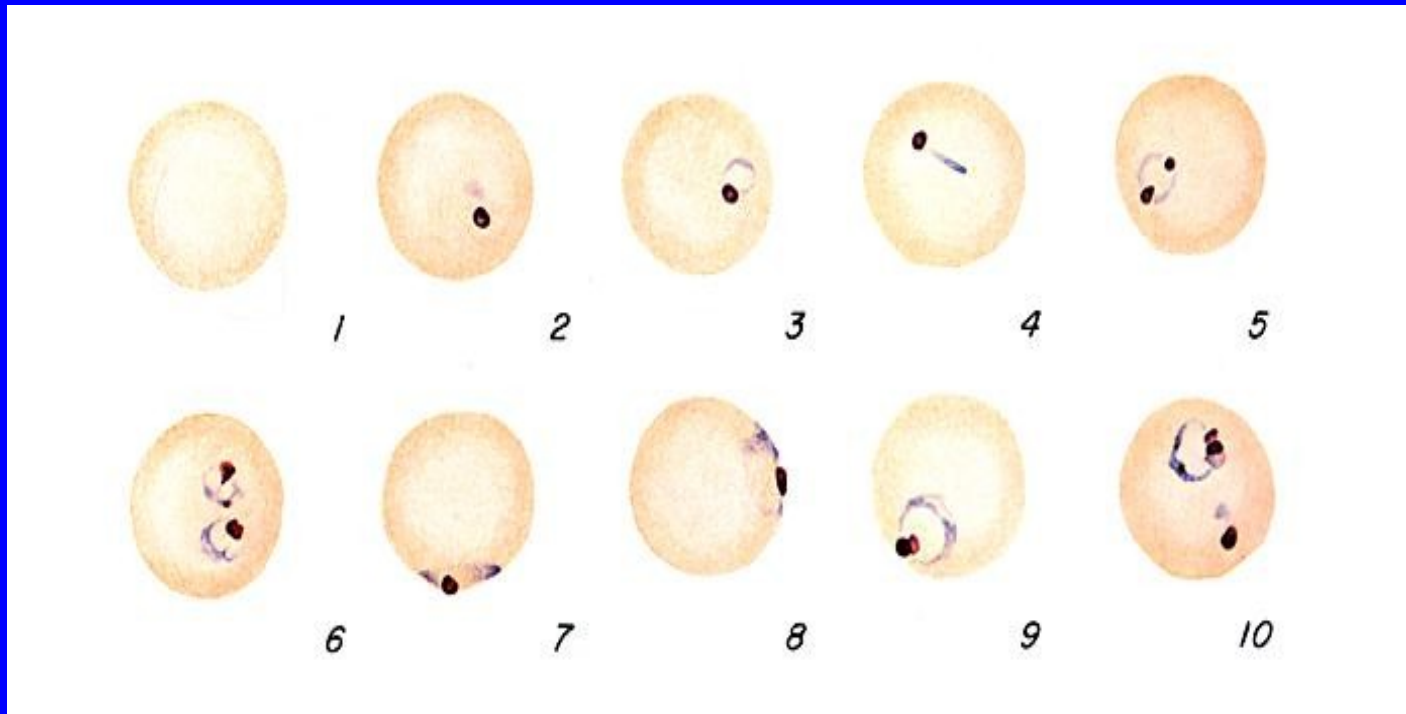
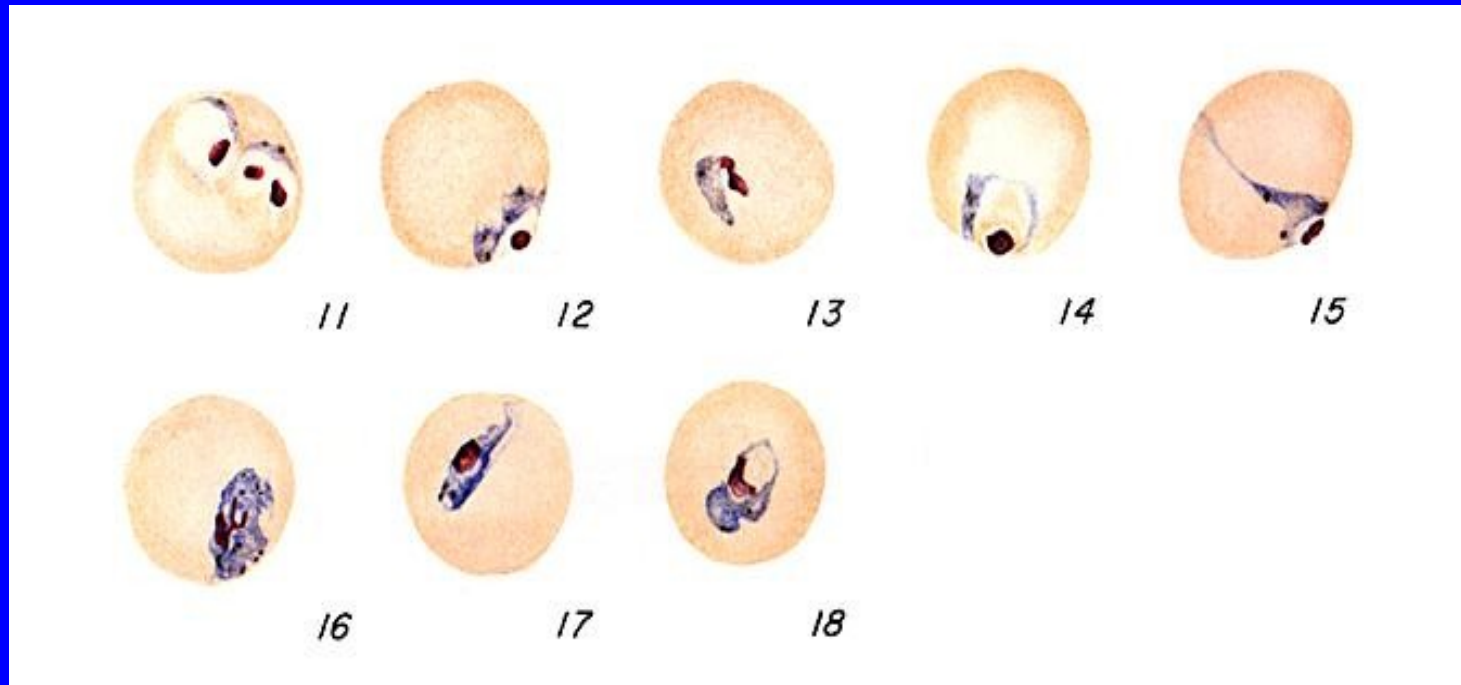


Fig. 13.31 Malaria. Very heavy parasitaemia in a patient with severe *P. falciparum* infection. Despite chemotherapy and exchange transfusion the patient died of cerebral malaria.

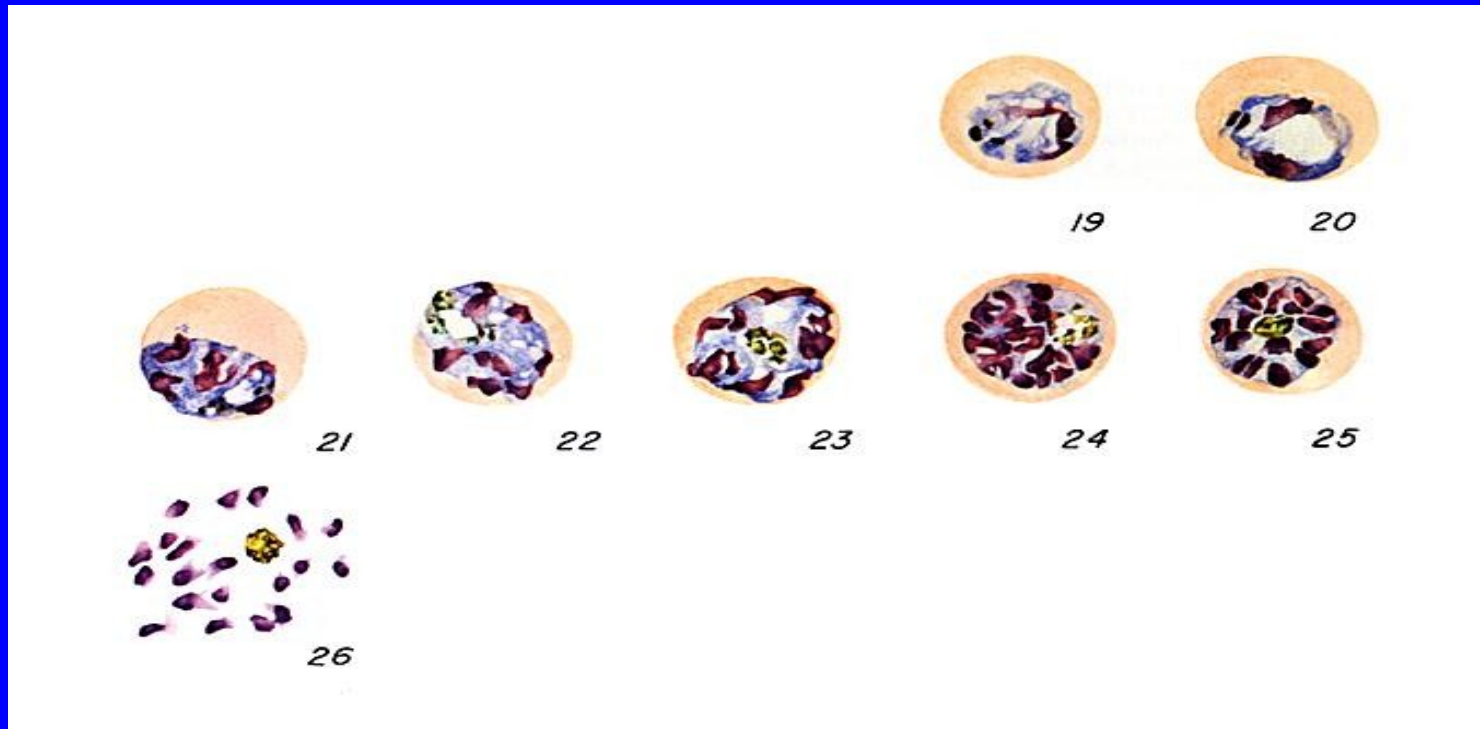
P. falciparum ring



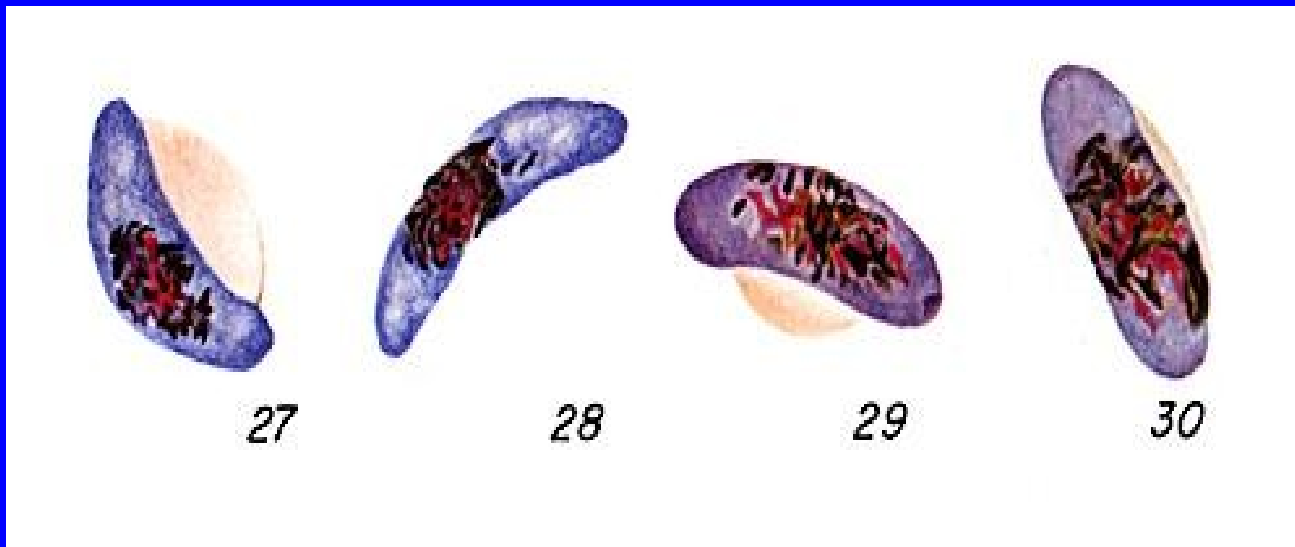
P. falciparum trophozoites



P. falciparum schizonts

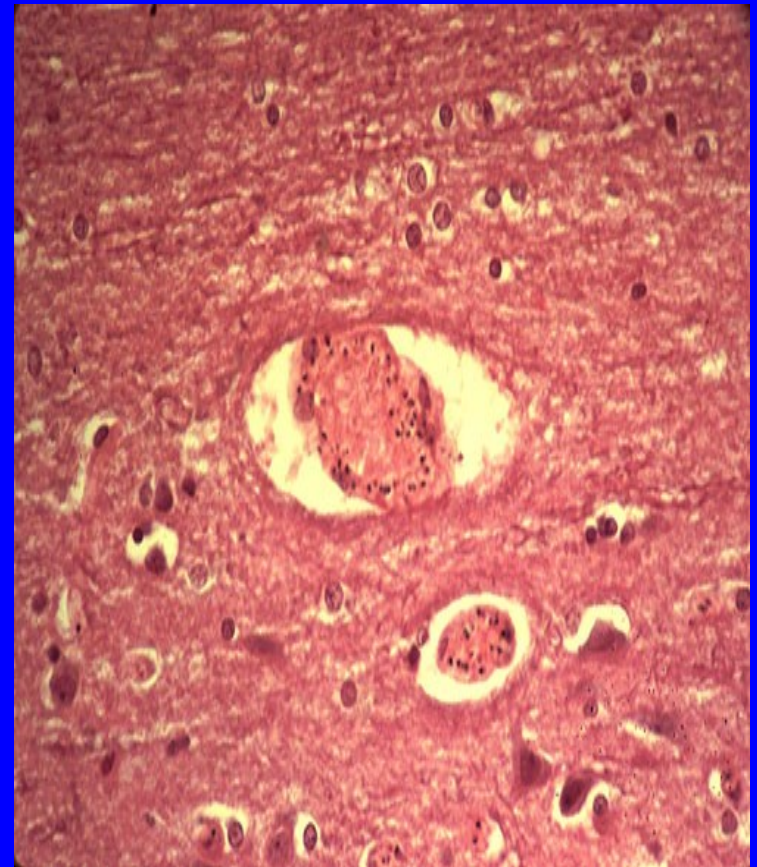


P. falciparum gametocytes



Cerebral Malaria

- Organism lining the inside wall of blood vessels
- Capillary congestion
- Perivascular hemorrhages
- Organisms stain brown-black



PERSONAL PROTECTIVE MEASURES

- To avoid mosquitoes
 - don't go
- Insect repellants
 - DEET - 20 - 35% lotion
 - Permethrin - spray on bed nets
- Mosquito nets
- Window screens/air conditioned rooms



Malaria in US Troops in Somalia

- 112 cases - Jan-Dec 1993
 - *P. vivax* (87%)
 - *P. falciparum* (7%)
- Risk factors
 - noncompliance with chemoprophylaxis - 56%
 - failure to use bed nets
 - failure to keep sleeves rolled down
 - guard duty along river > 7 nights

Malaria in US Troops in Liberia

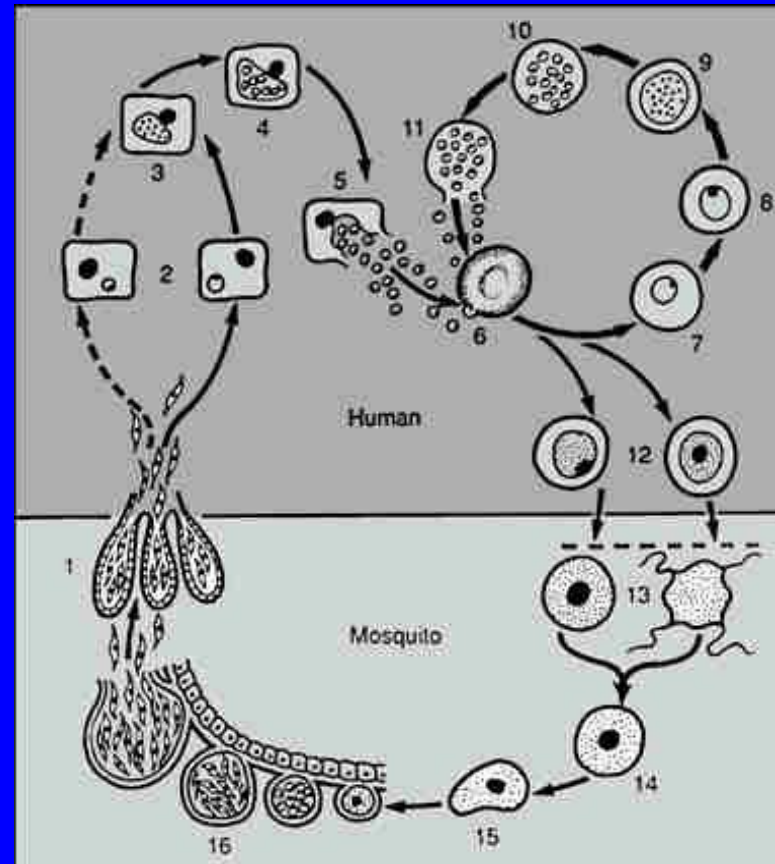
- 290 total JTF Personnel ashore in Liberia
- 80 malaria cases treated
 - 71 Marines, 7 Navy, 1 Army and 1 civilian
 - 51 cases confirmed by positive smear
 - 29 cases presumed by clinical criteria
 - Historical predicted risk is 11-50% for unprotected personnel
 - Personal Protective Measures
 - 7/133 (5%) (tested had protective levels of Mefloquine)
 - 19/290 (7%) surveyed had used DoD issued DEET formulation
 - 36/290 (12%) surveyed had permethrin treated uniforms
 - Bed nets were not carried ashore

VACCINE DEVELOPMENT

- Sporozoite antigens (CSP)
- Merozoite surface proteins (MSP)
- Erythrocyte binding antigen (EBA)
- Gametocyte antigens
- DNA based vaccines
- An effective vaccine will need at least three antigens

Plasmodium Life Cycle

- Trophozoites
 - 7,8. Ring
 - 9
- 10. Schizonts
 - Lyse RBCs
 - **11. Release merozoites**
- 12. Gametocytes
- 13-16. Cycle in vector



CHEMOPROPHYLAXIS

- 90% efficacious
- Compliance is poor
- Need to continue four weeks after returning
- Chloroquine - start two weeks before trip
- Mefloquine - start two weeks before trip
- Doxycycline - start two days before trip
- Primaquine - start after return - hypnozoites

CHEMOPROPHYLAXIS

- CHLOROQUINE - *ARALEN*
 - Once weekly in areas with sensitive organisms
 - 500 mg (salt)/300 mg (base)
 - GI upset, headache, blurred vision, myopathy
 - No serious eye damage reported
 - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- MEFLOQUINE - *Lariam*
 - Once weekly in Plasmodium sensitive areas
 - 250 mg weekly
 - GI upset, Insomnia, vivid or bad dreams
 - Neuropsych and spatial orientation problems
 - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- DOXYCYCLINE - *Vibramycin*
 - Daily in chloroquine/mefloquine resistant areas
 - 100 mg daily
 - GI upset, monilial vaginitis, photosensitivity
 - Not for use in children and pregnancy
 - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- PROGUANIL - *Paludrine*
 - Alternative to chloroquine/mefloquine resistant areas in Africa (not FDA-approved)
 - 200 mg daily combined with chloroquine
 - Anorexia, vomiting, diarrhea, mouth ulcers
 - Safe for use in children and pregnancy
 - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- PROGUANIL + ATOVAQUONE – *Malarone*
 - Prophylaxis for *P. falciparum*
 - Little data on *P. vivax*
 - 1 tab (100 mg + 250 mg) po qd with food
 - Take 2 days before travel, every day in malarious area and one week after return
 - Adverse effects: Abd. Pain – 17%, N/V – 12%, headache – 10%, asymptomatic ↑ ALT/AST

CHEMOPROPHYLAXIS

- PRIMAQUINE - *Primaquine*
 - Eradicates *P. vivax* or *P. ovale* from liver stage
 - 26.3 mg (salt)/15 mg (base)
 - Hemolysis in G6PD deficiency, GI upset
 - Not safe for use in pregnancy
 - Give for 2 weeks after leaving areas of high density parasites & risk - not for everyone

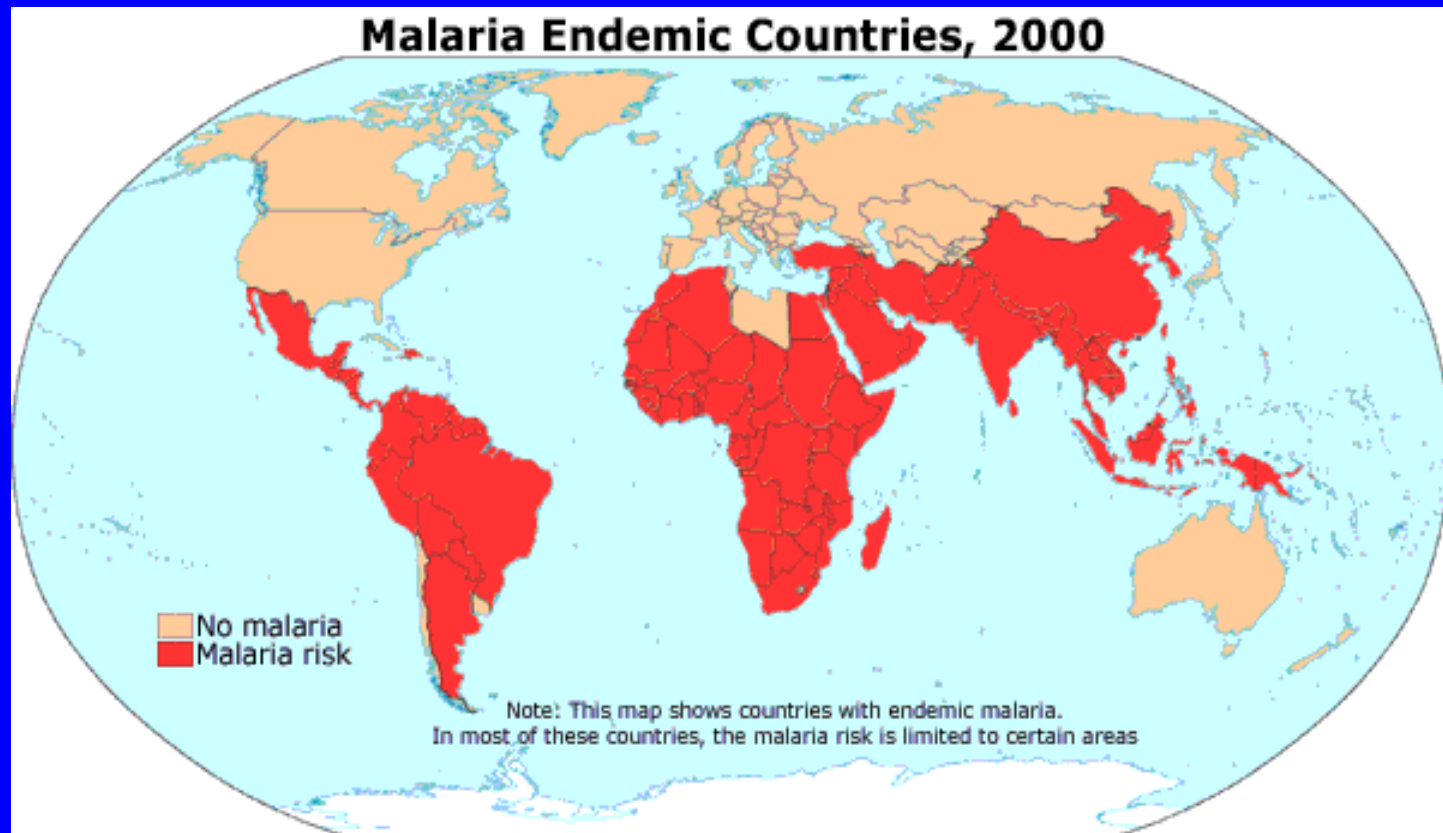
Classes of Anti-Malarial Medications

- **Blood Schizontocide**
 - Chloroquine, Quinine, Quinidine, Mefloquine, Halofantrine, Sulfonamides, Tetracyclines, Atovaquone, Artemisinin compounds
- **Tissue Schizontocide**
 - Primaquine, Proguanil, Pyrimethamine
- **Gametocide**
 - Primaquine
- **Hypnozoitocide**
 - Primaquine

TREATMENT

- Chloroquine
- Quinidine + doxycycline
- Mefloquine
- Fansidar - indigenous pop. or emergency
 - Three tabs po at one time
- Complete with 14 days of primaquine
 - May have had undetected dual infection

Geographic Distribution



CHLOROQUINE SENSITIVE

- Most non-falciparum species
- Caribbean
- Central America - not east of canal zone
- Middle East and Egypt
- Resistance seen in Papua New Guinea

CHLOROQUINE RESISTANT

- Most falciparum species
- Africa
- Southeast Asia - mefloquine resistance
- Central America - east of canal zone
- South America

Malaria

- Questions ?

